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TITLE: EFFECTS OF HYPOXIA ON THE VASOPRESSIN RESPONSE TO HEMORRHAGE AND ITS ROLE IN MAINTENANCE OF BLOOD PRESSURE

PRINCIPAL INVESTIGATOR: John R. Claybaugh, Ph.D.

CONTRACTING ORGANIZATION: Tripler Army Medical Center (HSC)
Tripler AMC, Hawaii 96859-5000

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John R. Claybaugh, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Tripler Army Medical Center (HSC)
Tripler AMC, Hawaii 96859-5000

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13. ABSTRACT (Maximum 200 words)

The research, conducted in conscious female goats, demonstrates for the first time that maintenance of blood pressure during hemorrhage is greatly compromised during conditions of hypoxia. This earlier reduction in blood pressure leads to an earlier increase in plasma levels of vasopressin but not plasma renin activity. Although these data would suggest a decrease in the baroreceptor-mediated renin release, subsequent experiments employing acute reductions in blood pressure by administration of sodium nitroprusside, did not confirm this. Thus, increases in renin were identical in response to 20% reductions in blood pressure whether or not 10% O_2 was administered. On the other hand, the sodium nitroprusside experiments demonstrated that baroreceptor-mediated vasopressin release was enhanced by hypoxia. The apparent reduced renin sensitivity to blood volume reduction in the hemorrhage experiments is presently theorized to be due to a decrease in sympathetic tone resulting from hypotension.

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FINAL REPORT

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4. PI John R. Claybaugh, PhD 5. Telephone No. (808) 433-5219

6. Agency Tripler Army Medical Center, Dept. of Clin. Invest.

7. Project Title: Effects of hypoxia on the vasopressin response to hemorrhage and it's role in the maintenance of blood pressure.

8. Current Staff, with percent effort on each project.

Mark Eichinger (100%)

John Claybaugh (20%)

9. Approximate PI expenditures to date:

Personnel $24,800 Supplies $6,547.75

Travel approx $4,363 Other

Equipment over $5,000 none

10. Comments on administrative and logistic matters.

In the original grant proposal $20,000 /year was anticipated for salary expenses, and the balance for TDY, supplies, and small equipment. Just as this MIPR was beginning, as stated in the quarterly reports, I had to discontinue training of one graduate student. Typical graduate student stipends are about $11,000/year now, and the student I discontinued was in the early part of his second year of graduate school, and I was paying him $800/month. I was unable to recruit a graduate student to replace him, and then we were faced with a hiring freeze, and I couldn't hire anyone. Toward the end of this grant period, I requested a no cost extension, which was approved through September 30th. The current graduate student, Mark Eichinger, should finish all of his thesis work and writing by December. Since the grant must end by september, I increased his pay for the months of July, August and September to $2,400/month, and he will work thereafter for nothing until he finishes his thesis. In this way we were able to obligate the money in approximate distribution as originally planned.

11. Scientific Progress:

There are essentially four subprojects to this grant. The original projects proposed the investigation of hemorrhage during hypoxia, and osmoregulation during hypoxia. To these, two more

have evolved in which influences of hypoxia on cardiovascular regulating endocrine systems in response to hypotension are being studied, and another in which angiotensin stimulation of vasopressin during hypoxia is being studied.

a. Hemorrhage during hypoxia: A major part of the thesis work of Mark Eichinger, has come from this study. Two very significant findings have emerged. These data demonstrate a greatly compromised ability to maintain blood pressure during hemorrhage when breathing hypoxic gas. The military significance of this is clear. Secondly, these data demonstrate a greatly inhibited response of renin to hypotension during hypoxia.

b. Effects of hypoxia on osmoregulatory systems: No progress was made due to loss of student after considerable training.

c. Effects of hypoxia on hypotension-induced changes in vasopressin, renin, ANF, and catecholamines. These are the final set of experiments that Mark Eichinger will do for his thesis work. He is about one-third of the way done with the experiments, so all methodology is in hand, but all data analysis and writing lie ahead. The proposed work has been approved by his thesis committee to satisfactorily fulfill requirements of the PhD.

d. Effects of hypoxia on angiotensin-stimulated vasopressin release. The release of vasopressin in response to osmotic stimuli is related to, and some investigators would say dependent upon, angiotensinergic mechanisms. We have refined and simplified the osmoregulatory experiments to investigate this first step, ie, the vasopressin reponses to intravenous and intracerbroventricular administration of angiotensin with and without concurrent hypoxia. These experiments are about 50% finished and will be completed by November. Currently the data suggest that intracerebroventricular injections of angiotenins are more effective in stimulating vasopressin during hypoxia. These are unexpected results, and in opposite direction to the responses we seem to be observing with intravenous infusions. There are many possibilities of explanation and significance, but it is too early to speculate further.

Publications: (Copies enclosed)

Claybaugh, J.R., A.K. Sato, and M.R. Eichinger. Blood pressure, AVP, ACTH, and PRA Responses to IV and IVT angiotensin II during hypoxia. Abstract submitted to 8th International Hypoxia Symposium, 1993.

Eichinger, M.R. Cardiovascular and Hormonal Responses to Hypotension During Hypoxia in the Conscious Goat. PhD Thesis, Biomedical Sciences (Physiology), University of Hawaii, Defended December 3, 1992. (a copy will be provided if requested, the Title and Acknowledgements pages have been included)

Eichinger, M.R., and J.R. Claybaugh. Hormonal responses to hypotension during hypoxia in the Conscious Goat. Abstract submitted to Experimental Biology (FASEB), 1993.

Eichinger, M.R., and J.R. Claybaugh. Hypoxia attenuates the renin response to hemorrhage. Am. J. Physiol. 263 (Regulatory Integrative Comp. Physiol. 32): R664-R669, 1992.

Eichinger, M.R., and J. R. Claybaugh. Hypoxic enhancement of the vasopressin response to hemorrhage. Physiologist 34:268, 1991 (abstract 52.10)

Eichinger, M.R., and J. R. Claybaugh. Cardiovascular and hormonal responses to hemorrhage during hypoxia. Proceedings of the 7th International Hypoxia Symposium, Lake Louise Canada, (Abstract #24), 1991.

Other:

The total grant was approximately $80,000 over 3 years. When the work is completed, it will have constituted the major support for the publications above, and also two more publications from the work in progress, and one PhD thesis. In addition, it has provided the stipend support for Mark Eichinger, who received top graduate student honors for two of the years during this grant period. It also provided stipend support for Robert Griffith who will most likely complete his masters degree next year.

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BLOOD PRESSURE, AVP, ACTH, AND PRA RESPONSES TO IV AND IVT ANGIOTENSIN II DURING HYPOXIA

Claybaugh, J.R., A.K. Sato, and M.R. Eichinger
Tripler Army Medical Center, Hawaii, USA 96859.

Chemoreceptor stimulation elicits a release of vasopressin (AVP) and adrenocorticotropic hormone (ACTH). AVP, ACTH, plasma renin activity (PRA), and blood pressure are controlled by central angiotensinergic mechanisms. Since angiotensin II (AII) is key to many of the salt and water regulating systems of the body, the responses of mean arterial blood pressure (MABP), AVP, PRA, and ACTH to either iv infusions (10 ng/kg/min) or intracerebroventricular (ivt) injection (150 ng in 200 ul) of AII in conscious female goats were studied during normoxia (NOR) and acute hypoxia (HYP; FiO_2 = 0.1). Increases in MABP were similar to ivt AII during NOR and HYP, but were reduced in response to iv AII during HYP. PRA was not affected in the ivt series, but was similarly reduced in response to iv AII during NOR and HYP. ACTH was only increased in reponse to ivt AII, and the response was not affected by hypoxia. AVP was increased by both iv and ivt AII, but the response to ivt AII was enhanced during HYP, with a sustained doubling in the magnitude of the increase in AVP. The MABP and ACTH responses to ivt AII do not suggest an increase in AII receptors or AII concentration in the CSF during hypoxia. The data suggest an attenuation of iv AII influence on MABP during hypoxia. Lastly, our results are compatible with a synergistic effect of chemoreceptor and central AII receptor stimulation of AVP.

Presenting Author: John R. Claybaugh
Address: Tripler Army Medical Center
Attn: HSHK-CI (Dr. Claybaugh), Tripler AMC, Hi Postal Code 96859-5000
Telephone No.: (808) 433-5219 (Area Code) Fax No.: (808) 839-6943 (Area Code)

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CARDIOVASCULAR AND HORMONAL RESPONSES TO HYPOTENSION DURING HYPOXIA IN THE CONSCIOUS GOAT

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAII IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN BIOMEDICAL SCIENCES (PHYSIOLOGY)

MAY 1993

By

Mark R. Eichinger

Thesis Committee:

John R. Claybaugh, Chairman
Yu-Chong Lin
Walter K. Morishige
Charles W. Weems
G. Causey Whittow

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I am most grateful tc my friend and mentor John R. Claybaugh. Through actions and words, you have taught me that honesty and integrity are the greatest traits a scientist can possess.

To my friends Aileen Sato, Glenn Hashiro, and Lola Tostado, I am thankful for all you have taught me in the laboratory, and the kind support you have provided during my training period.

To Michelle, my best friend and wife, I thank you for the love and understanding provided me on a daily basis. You have shared in the joys and frustrations of the last five years, and have given me the encouragement to continue.

Finally, I would like to recognize the financial support provided by The U.S. Army Health Services and Medical Research and Development Commands.

EXPERIMENTAL BIOLOGY 93

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HORMONAL RESPONSES TO HYPOTENSION DURING HYPOXIA IN THE CONSCIOUS GOAT. M. R. Eichinger and J. R. Claybaugh. Dept. of Physiology, Univ. of Hawaii, and Tripler Army Medical Center, Honolulu, HI. 96859-5000.

Plasma concentrations of arginine vasopressin (AVP), plasma renin activity (PRA), atrial natriuretic factor (ANF), norepinephrine (NE) and epinephrine (EPI) were assessed before and during sodium nitroprusside (SNP) induced hypotension in adult conscious female goats under normoxic (NH, n=4) or acute hypoxic (FiO_2=0.10; HH, n=4) conditions. After 60 min of normoxia or hypoxia, a 10 min SNP infusion was initiated to reduce MABP 20%. Hypoxic exposure alone was associated with an increase in heart rate (HR; 65 ±3 to 97 ±5 bpm; $p<0.05$) with no change in mean arterial blood pressure (MABP), or any of the plasma hormones. SNP induced hypotension increased HR from 67 ±5 to 103 ±9 bpm during normoxia, but had no effect on HR during hypoxia. AVP was increased with SNP infusion during both NH and HH periods, with HH values 5-fold greater than NH at both 5 and 10 min of hypotension ($p<0.05$). PRA and EPI were increased with SNP infusion during both NH and HH periods, with no measurable differences between conditions. ANF and NE were unchanged with SNP infusion. Thus, we conclude that hypoxia augments the AVP response to SNP induced hypotension. Additionally, it appears that acute hypoxia attenuates the baroreceptor reflex tachycardia to hypotension in the conscious goat.

Funded by US Army Health Services and Medical Research and Development Commands.

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M. R. Eichinger
2655 Peter St.
Honolulu, HI. 96816

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Hypoxia attenuates the renin response to hemorrhage

MARK R. EICHINGER AND JOHN R. CLAYBAUGH
Department of Physiology, University of Hawaii, Honolulu 96822; and Department of Clinical Investigation, Tripler Army Medical Center, Honolulu, Hawaii 96859-5000

Eichinger, Mark R., and John R. Claybaugh. Hypoxia attenuates the renin response to hemorrhage. *Am. J. Physiol.* 263 (*Regulatory Integrative Comp. Physiol.* 32): R664-R669, 1992.—We studied hypoxia and hypotensive hemorrhage in conscious female goats. After control, goats continued an experimental period in normoxia or hypoxia [fractional inspired oxygen concentration (FI_{O_2}) = 0.10] for 120 min. After 60 min in the experimental period, a hemorrhage (0.5 ml·kg^{-1}·min^{-1} for 30 min) was initiated (normoxic hemorrhage, NH; hypoxic hemorrhage, HH). Heart rate (HR) increased 51 ± 18 beats/min with NH after 30 min of hemorrhage. HR increased 40 ± 10 beats/min after hypoxic gas introduction, with no further increase during HH. Mean arterial blood pressure (MABP) was reduced 23 ± 7 mmHg 30 min after completion of blood loss with normoxia but was reduced 23 ± 7 mmHg at 20 min of HH. Arginine vasopressin (AVP) was increased to 2.60 ± 2.08 and 160.40 ± 49.74 μU/ml after 10 and 20 min of HH, respectively, and was only increased after 30 min (87.33 ± 67.18 μU/ml) of NH. Unexpectedly, plasma renin activity (PRA) increased in parallel in both groups and was doubled at 30 min of hemorrhage. Atrial natriuretic factor was reduced to 8.8 ± 1.6 pg/ml by 10 min of NH and to 11.4 ± 3.3 pg/ml at 30 min of HH. Thus hypoxia leads to an earlier development of hypotension and increase in AVP with blood loss but may attenuate the PRA response to blood pressure reduction.

arginine vasopressin; plasma renin activity; atrial natriuretic factor

BOTH INTACT and sinoaortic-denervated animals have been shown to regulate blood pressure during hypoxia (22). Yet, more than 20 years ago, Heistad and Wheeler (16) demonstrated an inability to maintain blood pressure during simulated hemorrhage with hypoxia in humans. In their study, a level of lower-body negative pressure found to have no effect on mean arterial pressure under normoxic conditions led to hypotension when the subjects breathed hypoxic gas. Forearm vascular resistance was found to be increased with lower-body negative pressure alone, but hypoxic gas administration attenuated the reflex. This observation suggests that local vascular responses to hypoxia can override reflex cardiovascular adjustments to blood pressure. Further, it has been shown that chemoreceptor reflexes are augmented by systemic hypotension, as determined by ventilatory and circulatory responses (15). However, it seems that the interaction of chemoreceptor and baroreceptor reflexes may not be strong enough to offset the prevailing vasodilatation and hypotension associated with hypoxia and lower-body negative pressure.

The above observations suggest that the maintenance of blood pressure during a hemorrhage with hypoxia would be impaired compared with the normoxic condition. Thus a hemorrhage would produce a reduction in blood pressure with less blood loss during hypoxia than during normoxia. The response of pressure-regulating hormones, regulated themselves by baroreceptors, would be expected to respond differently between a hemorrhage with normoxia and hypoxia. However, to our knowledge, only two studies have investigated the combination of hypoxic exposure and blood loss on cardiovascular and hormonal responses in conscious animals (24, 25). However, the duration of hypoxic exposure in both studies was of at least 24 h, and cardiovascular and hormonal responses to the blood loss were assessed only after completion of the hemorrhage. The intent of the present study was to further investigate the cardiovascular and hormonal responses during hemorrhage under acute hypoxic exposure. We hypothesized that hemorrhage during hypoxia would lead to both an earlier development and greater degree of hypotension and that hormones regulated by pressure changes would thus also show altered responses.

METHODS

Surgical preparation. Female goats (wt = 30-47 kg) were used in this study, which was approved by the Tripler Army Medical Center Institutional Animal Care Use Committee. At least 3 wk before use in experimental procedures, the right carotid artery was surgically brought to the surface of the neck and exteriorized in a loop of skin. Preanesthetic administration consisted of ketamine (10 mg/kg) and xylazine (0.2 mg/kg). Goats were maintained on halothane (0.5-1.5%) and O_2 (3 l/min) for the duration of the surgery. Under sterile operating conditions, a 10-cm incision was made midline about the midcervical area of the ventral side of the neck. A second parallel incision, 5 cm in length, with the same midpoint, was made 2.5 cm to the right of the first. The carotid artery was isolated and freed of its sheath. The vagus nerve was then carefully teased away from the artery and left intact in its original location. The strip of skin was teased away from the underlying muscle and was stripped of excess fat and connective tissue. Finally, the artery was enclosed in the skin flap produced by the two incisions and was sutured closed. No internal suturing was required, but tension sutures were used to oppose the two outside edges of the incisions before suturing. All loops remained patent for the duration of the study.

Experimental protocols. The goats were placed in a stanchion on the day before the experiment and were fasted overnight with water ad libitum. At about 8:00 A.M. a catheter (Novalon, 20 gauge, Deseret Medical) was inserted into the carotid artery loop to allow for measurement of mean arterial blood pressure (MABP) and heart rate (HR), as well as removal of arterial blood for samples and the hemorrhage procedure. In addition, an intravenous catheter was placed in the saphenous vein for an infusion site. Goats remained standing in the stanchion for the duration of the study and were fitted with a large box about the head for gas administration. Gases were delivered to the box from compressed gas cylinders; compressed air was delivered for the control and normoxic time periods, and compressed air mixed with nitrogen was delivered for the hypoxic periods. Fractional inspired gases were monitored with a Horizon Metabolic Cart. Arterial blood gases were measured using standard electrodes (Corning blood gas analyzer, model 168) and were corrected for body temperature. MABP and HR were monitored using a Hewlett-Packard pressure transducer and monitor (model 66).

Four experimental protocols were conducted. In a nonhemorrhaged control series, the goats breathed normoxic air for 60 min after catheterization. They then either continued with normoxic exposure or were exposed to 10% O_2 for an additional 120 min; these served as the normoxic control (NC) and hypoxic control (HC) experiments, respectively. In the other two protocols a 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ hemorrhage was initiated 60 min after control period and terminated 90 min after control period. These served as the normoxic hemorrhage (NH) and hypoxic hemorrhage experiments (HH). Each animal ($n = 5$) participated in all four protocols, performed on different days. One animal was unable to complete the HH protocol in two attempts and so is not included in this report (i.e., for HH, $n = 4$). At least 2 wk were allowed to pass after either a NC or HC study, and at least 3 wk after a hemorrhage study.

During the hemorrhage, arterial blood was withdrawn with a peristaltic pump (Sage model 375A) and was collected in sterile blood donor bags. The hemorrhaged blood was filtered (Travenol Laboratories) and reinfused on completion of the study period. Thirty-milliliter blood samples were withdrawn after the control period and at 60 and 120 min of gas exposure in the NC and HC groups; an infusion of 30 ml of isotonic lactated Ringer solution was made simultaneous to the removal of blood samples. Blood samples were also taken at 10, 20, and 30 min of hemorrhage in the NH and HH groups. The volume of these samples was incorporated into the hemorrhage and was removed at the predetermined hemorrhage rate. A portion of each sample (20 ml) was placed in iced heparinized tubes for later determination of plasma arginine vasopressin (AVP) and osmolality. The remainder of the blood was placed in iced Na-EDTA tubes for determination of plasma renin activity (PRA) and plasma atrial natriuretic factor (ANF) concentration. Two-milliliter plasma aliquots for ANF were treated with 50 μl aprotinin (10,000 KIU/ml).

Blood measurements. AVP was measured from extracted plasma utilizing previously described methods (12) and is reported in microunits per milliliter (~2.5 pg/μU). Because of low plasma concentrations, control AVP samples were extracted from 4 ml of plasma, diluted with 0.4 ml assay buffer, and assayed entirely. The within-assay coefficient of variability (CV) was 4% for the assay of these nonduplicated samples. Hemorrhage samples were assayed in multidose fashion with a within-assay CV of 9%. Between-assay CV was 6% for both methods. Osmolality was measured by freezing point depression osmometer (Advanced DigiMatic model 3D2). PRA and ANF were measured using commercially available radioimmunoassay kits (New England Nuclear and Peninsula Laboratories, respectively). Within- and between-assay CVs for PRA were 11 and 8%, respectively. Within- and between-assay CVs for ANF were 3 and 15%, respectively. Hematocrit (Hct) was determined by microcapillary centrifugation.

Statistical analyses. Our original statistical design was to utilize a two-way analysis of variance (ANOVA) for repeated measures with all data. However, we were unable to achieve an equal number of subjects in our hemorrhage groups. Because the difference in group size was due to the treatment effect per se (i.e., hemorrhage with hypoxia), we feel unjustified in utilizing the original statistical design (30). Therefore, each group was analyzed with a separate one-way ANOVA. A Duncan's multiple range test was performed to establish significance between means within each group. Corresponding time points between groups were compared with a two-tailed, unpaired t test. For consistency, control data were handled in an identical manner. Because of heterogeneity of variance in the hemorrhage AVP data, values were converted to $\log_{10}$ before statistical comparisons were made. Significance was set at $P < 0.05$.

RESULTS

Cardiovascular, blood gas, and hormonal responses to 120 min of normoxic or hypoxic gas exposure are given in Tables 1 and 2. Exposure to a fractional inspired O_2 concentration (FI_{O_2}) of 10% resulted in an expected increase in HR ($P < 0.01$), while MABP remained unchanged. Arterial O_2 partial pressure (Pa_{O_2}) was reduced to an average of 35.2 ± 2.0 mmHg for 120 min of hypoxic exposure. Likewise, arterial CO_2 partial pressure (Pa_{CO_2}) was reduced to 32.0 ± 1.1 mmHg, and pH increased to 7.44 ± 0.02. Hct was increased from 30.4 ± 1.2 to 33.9 ± 0.9% ($P < 0.01$) in the HC animals while plasma osmolality remained unchanged (290.8 ± 2.0 mosmol/kgH_2O).

Hypoxic gas exposure elicited no significant changes in any of the hormones measured. It was not possible to detect AVP in two NC and HC goats, and thus the lowest detectable limits for the assay (0.06 μU/ml) were substituted for these two individuals in the analyses.

Cardiovascular and hormonal responses to hemorrhage are presented in Figs. 1 and 2. In the NH group, HR was significantly greater than baseline ($P < 0.01$) only at the 30-min period of blood loss (*time 90*). At 30 min posthemorrhage (*time 120*), however, HR was no longer different from *time 0*. HR was increased by hypoxic exposure ($P < 0.01$) in the HH group and thereafter remained unchanged until the 30-min point of blood loss (*time 90*). At this point, HR was not significantly different from prehypoxia exposure; HR was again increased 30 min posthemorrhage (*time 120*).

MABP was significantly decreased during the posthemorrhage period in the NH group (to 75 ± 5 mmHg; $P < 0.05$). In contrast, MABP was decreased at 20 min of hemorrhage (*time 80*; to 75 ± 4 mmHg; $P < 0.01$) and stayed decreased in the HH group. MABP was not different between the two groups at either the 30-min point of hemorrhage or the posthemorrhage period (*time 90* and *time 120*, respectively).

While AVP was not increased until 30 min of hemorrhage (*time 90*) in the NH group (to 87.33 ± 67.18 μU/

Table 1. *Cardiovascular and blood gas responses in normoxic and hypoxic controls*

	Time, min			
	0	60	90	120
HR, beats/min				
NC	55±4	57±5	57±4	58±6
HC	59±5	121±12*†	103±12*†	95±12*†
MABP, mmHg				
NC	94±2	96±2	95±2	96±4
HC	100±3	98±3	99±4	99±4
Pa_{O_2}, mmHg				
NC	94.4±2.2	99.2±2.3	98.3±2.0	100.1±0.8
HC	97.4±2.3	32.7±2.1*†	35.9±2.1*†	37.0±2.4*†
Pa_{CO_2}, mmHg				
NC	36.5±1.6	35.4±1.1	36.6±0.8	36.8±0.5
HC	36.0±0.9	33.1±1.5*	31.1±1.1*	30.7±0.6*†
pH				
NC	7.42±0.02	7.43±0.01	7.42±0.01	7.42±0.02
HC	7.41±0.02	7.43±0.01*	7.44±0.01*	7.44±0.02*

Values are means ± SE; $n = 5$ for normoxic control (NC) and hypoxic control (HC). HR, heart rate; MABP, mean arterial blood pressure; Pa_{O_2}, arterial O_2 partial pressure; Pa_{CO_2}, arterial CO_2 partial pressure. * $P < 0.05$ vs. *time 0*; † $P < 0.05$ vs. NC.

Table 2. *Hormonal responses in normoxic and hypoxic controls*

	Time, min		
	0	60	120
AVP, μU/ml			
NC	0.17±0.07	0.17±0.07	0.16±0.06
HC	0.19±0.06	0.17±0.06	0.18±0.06
PRA, $ng \cdot ml^{-1} \cdot h^{-1}$			
NC	0.78±0.11	0.76±0.13	0.84±0.07
HC	1.12±0.27	1.34±0.31	1.32±0.38
ANF, pg/ml			
NC	15.6±1.2	14.2±2.0	13.1±1.0
HC	12.9±2.6	14.5±1.7	13.5±2.0

Values are means ± SE. AVP, arginine vasopressin; PRA, plasma renin activity; ANF, atrial natriuretic factor.

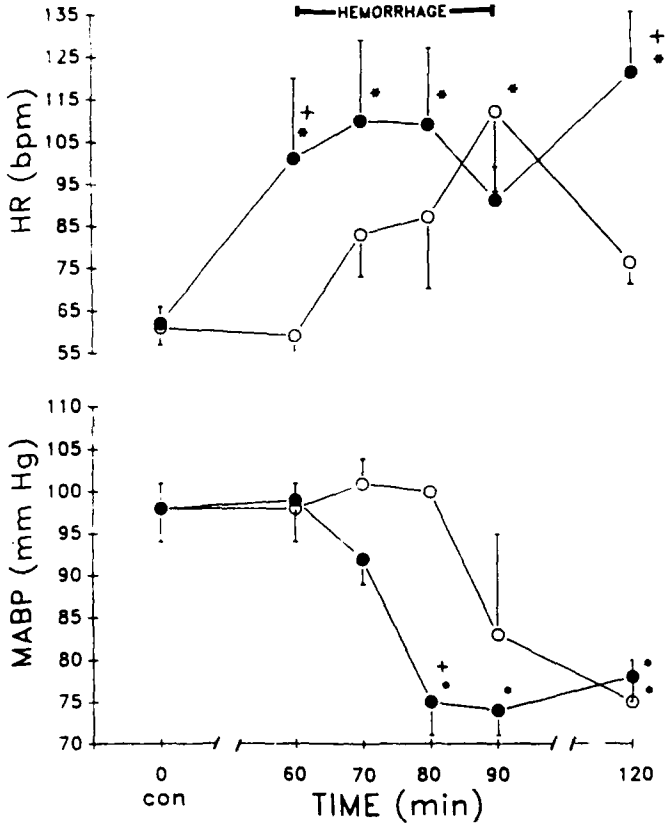

Fig. 1. Cardiovascular responses to hemorrhage during normoxia ($n = 5$, open circles) and hypoxia ($n = 4$, solid circles). * $P < 0.05$ vs. *time 0*. + $P < 0.05$ vs. corresponding normoxic hemorrhage (NH) time. HR, heart rate; MABP, mean arterial blood pressure.

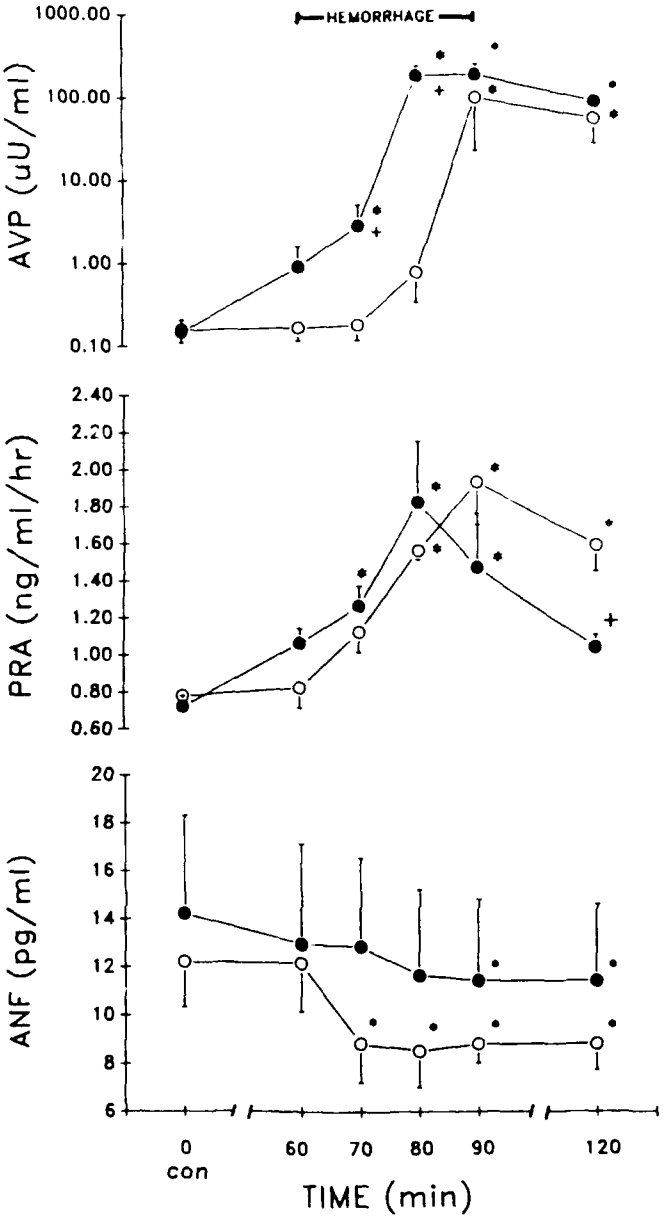

Fig. 2. Hormonal responses to hemorrhage during normoxia ($n = 5$, open circles) and hypoxia ($n = 4$, closed circles). Note log scale for arginine vasopressin (AVP). PRA, plasma renin activity; ANF, atrial natriuretic factor. * $P < 0.05$ vs. *time 0*; + $P < 0.05$ vs. corresponding NH time.

ml), it was significantly increased above control and corresponding NH values at 10 and 20 min of blood loss (*time 70* and *time 80*) in the HH group (2.60 ± 2.08 and 160.40 ± 49.74 μU/ml, respectively). Both groups showed increased AVP levels at 30 min of hemorrhage (*time 90*) and posthemorrhage (*time 120*), although there were no significant differences between groups at those time points.

The initial PRA response to hemorrhage was similar in the two groups, with an increase evident at 10 min of hemorrhage (*time 70*) in the HH group. Both groups showed a continued increase in PRA as the hemorrhage progressed, although it is apparent that at 30 min of blood loss (*time 90*) the PRA in the HH group was starting to decline. Indeed, during the posthemorrhage period there was a significant difference in PRA between the two groups, with the HH value no longer greater than its control. The NH PRA value remained significantly greater than its control after the blood loss (*time 120*).

ANF was decreased and stayed reduced after 10 min of hemorrhage (*time 70*) in the NH group and 30 min of blood loss (*time 90*) in the HH group. However, there were no differences between groups at any time point.

DISCUSSION

We hypothesized, based on the findings of Heistad and Wheeler (16), that hemorrhage during hypoxia, compare

with normoxia, would result in an earlier development of hypotension and that, consequently, vasoactive hormones would respond differently. Our results support this hypothesis.

The cardiovascular and hormonal responses to hypoxic exposure are well documented. Several studies, incorporating a level of hypoxia similar to ours, have demonstrated an increased heart rate with no change in MABP (1, 16, 22). While studies have shown an increase (11, 26) or a decrease (7, 23) in AVP with hypoxic exposure, in the present studies it is apparent that the conscious, spontaneously breathing goat, in similar fashion to human subjects (7), exposed to moderately severe hypoxia shows no change in plasma concentration of this hormone. This response, too, has previously been reported (2, 29). Likewise, PRA (2, 8) and ANF (5) have been shown to be unaffected by hypoxic exposure. In light of findings by others, the cardiovascular and hormonal responses to hypoxia we observed are not unique.

Several investigators (3, 4) have demonstrated an increased baroreceptor reflex sensitivity with hypoxia. Further, Bagshaw and co-workers (4) presented evidence that mild hypoxemia maximized the ability of the carotid sinus reflexes to maintain arterial pressure. Thus it appears hypoxic exposure may increase the ability of the cardiovascular system to reflexively control cardiovascular function. Our findings, however, are similar to the studies by Heistad and Wheeler (16) and suggest that despite the possible increased baroreceptor reflex sensitivities, hemorrhage represents a greater cardiovascular challenge during acute hypoxia. It is generally agreed that local vascular hypoxemia elicits vasodilation, while chemoreceptor reflexes act to maintain blood pressure and flow (14). Also, the increased HR and unaltered MABP associated with hypoxia in our study would suggest that cardiac output was increased in our animals. Despite this probable occurrence, hypotension developed within 20 min of blood loss during hypoxia, about a 12.5% blood volume reduction assuming a blood volume of ~80 ml/kg.

Figure 1 clearly illustrates the time course difference in the development of hypotension between the two conditions. The period from *time 60* to *time 80* is of special interest because during HH a reduction in MABP of >24 mmHg occurred, while MABP remained unchanged during NH. The difference in MABP between the two conditions was no longer apparent at 30 min of blood loss (*time 90*) or posthemorrhage (*time* 120), indicating that although hypotension develops sooner during HH, the magnitude of pressure reduction with blood loss during hypoxia is no greater than with normoxia. In question, then, is the relative contributions of local vascular effects, cardiovascular reflexes, and hormonal systems in the regulation of blood pressure under the two O_2 states.

In two other studies investigating the combination of hypoxia and hemorrhage on hormonal and cardiovascular responses (24, 25), no differences were observed in blood pressure between a normoxic and hypoxic group of rats after blood loss. However, neither study assessed the blood pressure response during hemorrhage. The earliest measurement of blood pressure after hemorrhage was taken 10 min after the onset of blood loss (25). Thus it was not possible to determine the rate of change in blood pressure between the two groups. It is interesting to note we also did not observe a difference in MABP between groups after completion of hemorrhage (Fig. 1). Finally, the relative reductions in blood volume (~20%) appear to be similar between our study and those of Raff et al. (24, 25). However, in the studies by Raff et al., experimental design dictated a rapid withdrawal of blood (over 1 and 2 min; Refs. 24 and 25, respectively), perhaps precluding any observable differences in cardiovascular responses to hemorrhage during normoxia and hypoxia as we have demonstrated.

Like the MABP changes we observed, the AVP responses to hemorrhage differ with regard to time. It appears the AVP responses follow MABP changes, although this is not entirely certain. In both hemorrhage conditions, plasma AVP levels were significantly greater before a significant reduction in MABP was noted. However, it is also clear that MABP was tending toward reduction in both groups at the point of increased AVP. Such a finding is in agreement with others (19) and would suggest "normal" arterial baroreceptor regulation of AVP. Thus it appears that the high-pressure arterial baroreceptors may be primary regulators of vasopressin secretion during hemorrhage in the goat. Seemingly, then, the conscious goat behaves in much the same manner as has been described in the conscious dog by Cowley et al. (9). In their dogs, blood loss that reduced atrial pressures without reduction in arterial pressures produced only mild increases in AVP. Constrictor levels of the hormone were not observed until hypotension developed.

Yet it could also be argued that low-pressure cardiac baroreceptors (i.e., left atrium) play a role in the release of AVP during hemorrhage with normoxia or hypoxia. The significant increase in plasma AVP levels before a MABP reduction would support this argument (13). However, as no cardiac pressures were measured in the present study, the possibility of low-pressure baroreceptor involvement remains an unresolved issue. AVP concentration plateaued in both groups, and final concentrations were not different between groups. Because final MABP was not different between NH and HH, it could be suggested that the main stimulus for AVP release during a hemorrhage with normoxia or hypoxia is indeed a reduction in arterial blood pressure.

In contrast to our findings, Raff et al. (25) demonstrated a hypoxic enhancement of AVP 20 min posthemorrhage. The greater increase in AVP observed following hemorrhage with hypoxia in their study occurred despite a blood pressure reduction similar to a group hemorrhaged during normoxia. The authors were unable to account for the observed differences in AVP, although they suggested a possible interaction of baroreceptor and chemoreceptor stimuli (25).

In a comprehensive review article, Korner (18) has cited numerous studies that indicate that hypoxia is capable of resetting the baroreceptor reflexes in conscious animals. Further, Heistad et al. (15) have shown an enhancement of chemoreceptor control of ventilation during hypoxic exposure with hypotension. At least one

study (1) has proposed that baroreceptor stimulation of vasopressin is responsible for the antidiuresis and decrease in free water clearance associated with hypoxia. While these findings might suggest a possible hypoxic enhancement of baroreceptor regulation of AVP, our data do not conclusively support such a notion. A regression analysis comparing the slopes of AVP with arterial blood pressure in NH and HH was not statistically significant ($P < 0.1$)

PRA responses to hemorrhage were affected by hypoxia. The PRA response during NH and HH were essentially parallel, with the HH group showing an earlier significant increase. The first significant increases in PRA occurred 20 min before a decrease in MABP with NH, and 10 min before with HH. Most curious is the nearly identical responses of PRA to hemorrhage during normoxia and hypoxia, especially considering the earlier development of hypotension during HH. Again, referring to the first 20 min of blood loss (i.e., *time 60* to *time 80*), it should be noted that during HH a reduction in MABP of ~24 mmHg was observed, while MABP was unchanged during NH. After the same 20-min time period, however, there was no difference in the PRA responses between the two experimental conditions (NH 1.56 ± 0.05 vs. HH 1.82 ± 0.33 $ng \cdot ml^{-1} \cdot h^{-1}$). There are many known stimuli for the release of renin including a reduction in renal blood flow or perfusion pressure and increased renal sympathetic nerve activity (17). The exact mechanism behind the hypoxic moderation of renin release is unclear and might involve a moderation in renal blood flow, low-pressure cardiac baroreceptors, or renal sympathetic nerve traffic or effectiveness.

Thirty minutes posthemorrhage, PRA measurements were lower during HH than NH. Because during HH the AVP responses at 10 and 20 min of hemorrhage were greater than during NH, AVP may have suppressed renin secretion. Several investigators have shown AVP inhibition of renin release, most at concentrations far lower than we measured (17, 21, 27, 28). Regardless of the cause for the drop in PRA seen after hemorrhage, it is apparent that increased activity of the renin-angiotensin system need not be present to maintain blood pressure after a hemorrhage with hypoxia.

Finally, ANF was decreased during hemorrhage in both normoxic and hypoxic conditions, although the time periods for the reduction were different. During NH a reduction after 10 min of blood loss was observed, while HH showed a reduction after 20 min of hemorrhage. The interpretation of ANF responses to hemorrhage is difficult, as investigators have shown both decreases (10) and increases (6) after blood loss. The apparent delay in the ANF reduction in the HH group could be due to a variety of factors. It is plausible that hypoxia is acting as a stimulus to ANF, preventing a reduction of similar magnitude observed with NH. While this idea has been proposed by Lew and Baertschi (20), our hypoxic control data do not support this as we could not demonstrate an increase in ANF with 120 min of hypoxic exposure. A more likely explanation is provided by Carlson and co-workers (6), who have hypothesized that atrial tachycardia may indirectly be responsible for ANF release. The authors theorized that rapid atrial contractions may have elicited ANF release because increased atrial pressures developed, presumably because of contractions against a closed valve during ventricular systole. The idea of brief, increased atrial pressure stimulation of ANF partially offsetting the inhibitory effects of reduced central blood volume is feasible, although we have no direct evidence to support such a notion.

In conclusion, our data indicate that hypoxia leads to an earlier development of hypotension because of hemorrhage. Although the development of hypotension may be the primary stimulus for AVP secretion during hemorrhage with normoxia or hypoxia in the conscious goat, the role of low-pressure baroreceptor mechanisms in this response remains unclear. Further studies designed to include the measurement of cardiac pressures and cardiac output are justified. Despite the earlier development of hypotension due to blood loss during hypoxia, PRA responds in a fashion similar to a hemorrhage with normoxia. Thus it appears hypoxia attenuates the PRA response to hypovolemia. The earlier onset and higher levels of circulating AVP during hypoxic hemorrhage may in part be responsible for the decrease in PRA observed during hypoxic hemorrhage despite the continuation of hypotension. Finally, ANF has been shown to decrease with hemorrhage in both hypoxic and normoxic conditions, although at a later time period with hypoxia.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Address for reprint requests: Commander, Tripler Army Medical Center, Attn: HSHK-CI/J. R. Claybaugh, Tripler AMC, Hawaii 96859-5000.

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52.5

THE EFFECT OF CREATINE DEPLETION AND ENDURANCE TRAINING UPON WORK CAPACITY AND CARDIAC FUNCTION. R.P Farrar*, D.Bowles*, H. Park*, H.L.Sweeney*, and J.W.Starnes*, (SPON: J.Wilmore) Dept. of Kinesiology, Univ. of Texas, Austin, TX. 78712 and Dept of Physiology, Univ. of Penn.

F344 male rats were placed in one of two main groups, creatine depleted or control diet, and then each group further subdivided into sedentary, endurance or interval trained groups. The treatments were evaluated in terms of *in vitro* heart function, myosin isozyme composition, citrate synthase, changes in *in vivo* work capacity (VO_2) and run-time to exhaustion. Creatine depletion, achieved through feedings of 3% ß-guanidinopropionic acid(ßGPA) in the diet, had no effect upon VO_2max when compared to their contol-diet matched groups. Creatine depletion doubled the run-to-exhaustion time in the sedentary group, reduced it significantly in the endurance group, and had no effect on the interval group, relative to the control-diet matched groups. ßGPA feeding did not alter the citrate synthase activity nor myosin isozyme patterns of the heart when compared to their control-diet matched groups. Significantly lower cardiac outputs were observed in all ßGPA treated groups when the hearts were evaluated against 130mm Hg afterload and paced at 420bpm in the working heart model. The interval trained ßGPA hearts had significantly higher cardiac outputs than all other ßGPA groups. Creatine depleted hearts appear unable to meet the demands of high heart rate and high afterload *in vitro*. The interaction of creatine depletion and training resulted in cardiac hypertrophy, a normal training response in VO_2max, but only interval training attenuated the decline in cardiac outputs against a high heart rate and high afterload.

52.6

THE INTERACTION OF CHRONIC ß-GUANIDINOPROPIONIC ACID (ßGPA) FEEDING AND INTERVAL TRAINING UPON SKELETAL MUSCLE FUNCTION H. Park*, G.Howell, H.L.Sweeney* R.P.Farrar* (SPON: J. Ivy). Dept. of Kinesiology, Univ. of Texas, Austin, TX, 78712 and Dept. of Physiology, Univ of Penn.

Depletion of creatine by the feedings of ßGPA in the diet has been utilized to determine whether changes in the spatial and temporal buffering of the phosphorylation potential can induce changes in aerobic capacity of the muscle as well as expression of myosin isozymes. In order to exacerbate changes in the phoshorylation potential high intensity interval training, repeated sprints of 60m./min, was imposed upon F344 male rats that were placed on a diet of 3% ßGPA. Following 12-15 weeks of this protocol the plantaris muscle was evaluated for changes in contractile, histochemical and biochemical properties. The interval training did not alter contractile function, but did increase citrate synthase activity by 50%. ßGPA feedings alone did not alter contraction time, half relaxation time or tetanic force, but the fatigue index was increased by 200%, while citrate synthase increased by only 25%. The interaction of the two increased contraction time and half relaxation time by 50%, increased fatigue index by 450%, decreased tetanic force by 60 %, but did not change specific tension. Histochemical analysis demonstrated that ßGPA feedings alone did not induce fiber type transformation, but that interval training caused a significant ($p \leq 0.05$) increase in type I fibers at the expense of type IIB fibers. The interaction of interval training and creatine depletion induced significant fiber type shifts with type IIB decreasing by 50%, type IIA increasing by 35%, and type I increasing by 100%. Interval training imposed upon creatine depleted muscles significantly increases the signals for fiber type transformation.

52.7

MODULATION OF HYPOXIC TOLERANCE BY NALOXONE AND MORPHINE IN MICE. Kimberly P. Mayfield and Louis G. D'Alecy*. The University of Michigan, Ann Arbor, MI 48109

Our laboratory has demonstrated that a non-lethal, hypoxic pretreatment increases hypoxic survival time (HST) in mice. To determine if endogenous opioids alter HST we administered naloxone (1 mg/kg i.p.) at minus 5 min, morphine (10 or 20 mg/kg i.p.) at minus 30 min, or saline (0.3 ml i.p.) at corresponding times prior to the hypoxic pretreatment. Sixty percent of the mice received the pretreatment consisting of three hypoxic exposures (4.5% oxygen balance nitrogen for 1.5, 2, and 2.5 min) separated by 5 minutes of room air. The remaining mice did not receive a pretreatment but instead were maintained on room air for this duration. All mice were tested for hypoxic survival by first exposing them to 20 sec of 8.5% oxygen balance nitrogen followed by exposure to 4.5% oxygen balance nitrogen. The HST was recorded as the time from the onset of the 4.5% oxygen to the cessation of spontaneous ventilation. Control mice (non-pretreated, saline injection) had a pooled mean HST of 147±9 sec (*n*=46). The pretreatment significantly increased HST ($p<0.001$, Mann Whitney U Test). Saline injected, pretreated mice had HST's of 434±61 sec (*n*=20, injected at minus 5 min) and 437±35 sec (*n*=49, injected at minus 30 min). Naloxone significantly ($p<0.01$) blunted the pretreatment effect producing a mean HST of 215±28 sec (n=17) which was not significantly different ($p=0.238$) from non-pretreated, saline-injected mice. Mice given 10 mg/kg morphine had an augmented pretreatment effect with a mean HST of 550±51 sec compared to pretreated, saline-injected mice. However, 20 mg/kg morphine dampened the pretreatment effect decreasing the mean HST to 353±31 sec which is a shorter survival time than the saline controls. These preliminary results suggest that endogenous opioids may be involved in the protective adaptation to hypoxia induced by prior exposure to non-lethal hypoxia.

52.8

HYPOCAPNIA, HIGH ALTITUDE, AND EGGSHELL CONDUCTANCE TO WATER VAPOR (GH_2O). S.C. Hempleman, F.L. Powell, T.P. Adamson*, and R.E. Burger*. U.C. San Diego, La Jolla, CA 92093-0623 and U.C. Davis, Davis, CA 95616.

We hypothesized that hypocapnia associated with high altitude hypoxia in hens is responsible for the reduced GH_2O in avian eggs. If true, correcting hypocapnia (but not hypoxia) at altitude should return GH_2O to normal values. Seven hens native to 1200m were exposed to high altitude (3800m), and then to high altitude with 28 torr $PICO_2$ to relieve hypocapnia (3800m+CO_2). Eggshell GH_2O was measured gravimetrically, shell thickness was measured micrometrically ($\bar{x}$±sem):

	1200m	3800m	3800m+CO_2
Number of Eggs	102	82	118
GH_2O (mg/d/torr)	13.9±.2	12.6±.2	11.1±.2
Thickness (mm)	.297±.003	.287±.003	.305±.003
Pore Area (mm^2)	1.97±.03	1.72±.03	1.61±.03

Relieving hypocapnia at altitude reduced both GH_2O and pore area of the eggshell ($p<.05$), thus we must reject our initial hypothesis. Other altitude stimuli (eg. hypoxia or hypobaria) may cause the reductions in eggshell GH_2O and shell pore area we observed at 3800m. Hypocapnia does appear to cause thinning of eggshells at altitude ($p<.05$). Supported by NIH grants HL17731 and HL02071.

52.9

OXYGEN CONSUMPTION OF THE AXOLOTL, *Ambystoma mexicanum*, AS A FUNCTION OF VENTILATORY MODE DURING A PROGRESSIVE HYPOXIC CHALLENGE. C. F. Zwemer* H. D. Prange* and J. M. Stager. Physiology Section, Medical Sciences Program, Indiana University, Bloomington, IN 47405.

Are different metabolic strategies employed when bimodal breathers are forced to ventilate exclusively through the aquatic mode? To address this question, we measured the oxygen consumption ($\dot{V}O_2$) in $ml \cdot g^{-1} \cdot hr^{-1}$ of 11 adult axolotls during progressive aquatic hypoxia (PO_2 from 150 to 0 mmHg). Aquatic and aerial $\dot{V}O_2$ was measured during 30 min exposure to different aquatic PO_2's. The relationship between $\dot{V}O_2$ and PO_2 was best represented by a quadratic regression where $\dot{V}O_2 = 0.10 - 1.04 \cdot 10^{-3} \cdot PO_2 + 3.70 \cdot 10^{-4} \cdot PO_2^2$ ($r=.83$) for axolotls with access to air. For those without access to air, $\dot{V}O_2 = -3.40 \cdot 10^{-3} + 2.93 \cdot 10^{-4} \cdot PO_2 - 7.43 \cdot 10^{-7} \cdot PO_2^2$, ($r=.91$). These regressions differ significantly ($p<.0001$) and diverge significantly, ($p<.0001$) below a PO_2 of about 90 mm Hg. These results demonstrate that, when challenged by aquatic hypoxia, VO_2 is a function of the availability of access to air and that metabolism may be depressed when axolotls are forced to breathe solely in water. (Funded in part by Indiana University Doctoral Student Grant-in-Aid)

52.10

HYPOXIC ENHANCEMENT OF VASOPRESSIN RESPONSE TO HEMORRHAGE. M. R. Eichinger * and J. R. Claybaugh. Tripler Army Med. Ctr., Hon., HI. 96859

Cardiovascular and hormonal responses to hemorrhage with hypoxia were studied in conscious goats. Following control, goats continued in normoxia (NH) or were exposed to hypoxia (HH, FiO2=10%) for 120 min. After 60 min of normoxia or hypoxia, a hemorrhage was initiated (0.05 ml/kg/min for 30 min). Mean arterial blood pressure (MABP) and heart rate (HR) were monitored throughout; arginine vasopressin (AVP), atrial natriuretic factor (ANF), and plasma renin activity (PRA) were assayed. MABP was maintained through 20 min of hemorrhage in the NH group, and then decreased by 30 min of blood loss. In contrast, MABP was reduced by 20 min of hemorrhage in the HH group and remained decreased. AVP responses mirrored MABP changes in the NH group with a significant increase simultaneous to MABP decrease. However, AVP was significantly elevated 10 min prior to a decrease in MABP in the HH group. Further, lowest MABP values were not different between the groups, yet AVP was two-fold higher in the HH group. PRA increased in parallel in both groups up to 20 min; at 30 min NH group was higher than HH group and remained higher post-hemorrhage. Hypoxia significantly attenuated the ANF reduction in response to hemorrhage. Thus, hemorrhage during hypoxia results in an earlier development of hypotension and enhances the AVP response to MABP reduction.

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23

ACUTE HIGH ALTITUDE ILLNESSES ARE NOT RELATED TO PERIODIC BREATHING AND APNEAS DURING SLEEP

U. Eichenberger, U. Waber, M. Maggiorini, O. Oelz, P. Bärtsch, University Hospital Zurich and Dep. of Medicine, Inselspital, CH-3010 Bern, Switzerland

The hypothesis was tested that periodic breathing and/or apneas during sleep at high altitude are more frequent and reinforce hypoxemia in subjects developing acute mountain sickness (AMS) and high altitude pulmonary edema (HAPE). Thoraco-abdominal movements and oxygen saturation were registered by Medilog recorders and Biox 3700 during the first night spent at 4559 m. Analyzable time was between 84 and 90 % of the total recording time (7 h) and not significantly different between subjects staying without AMS (AMS-), developing AMS (AMS+) or HAPE during a stay of 3 days at 4559 m. Median oxygen saturation (SaO_2), percentage (%) of analyzed time with periodic breathing (periodic) and apneas (>10 sec) were (means ± SD):

	n	SaO_2	periodic (%)	apneas (%)
AMS-	9	63 ± 10	59 ± 25	2.6 ± 5.0
AMS+	4	63 ± 7	67 ± 16	0.5 ± 0.7
HAPE	8	49 ± 10	75 ± 20	0.7 ± 1.3
p		< 0.025	ns	ns

These results show that SaO2 in AMS- and AMS+ is not different during sleep at high altitude. Furthermore, periodic breathing and apneas do not account for the significantly lower oxygen saturation observed in subjects developing HAPE.

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CARDIOVASCULAR AND HORMONAL RESPONSES TO HEMORRHAGE DURING HYPOXIA

Eichinger, M.R. and J.R. Claybaugh. Dept. of Physiology, University of Hawaii, and Dept. of Clinical Invest., Tripler Army Med. Ctr., Hon., HI 96859

Since hypoxia and hemorrhage each present special cardiovascular and hormonal challenges, we studied the combined effects in conscious goats. Following a control period, goats continued in normoxia or were exposed to hypoxia (FiO2=10%) for 120 min. After 60 min a continuous hemorrhage (.5 ml/kg/min for 30 min) was initiated (normoxia, NH,n=3;hypoxia HH,n=3). Blood pressure (MABP) and heart rate (HR) were monitored throughout; vasopressin (VP), plasma renin activity (PRA) and atrial natriuretic peptide (ANP) were assayed. HR increased in the NH group after 30 min of blood loss. HR increased after hypoxic gas introduction, but did not increase further in the HH group. MABP was reduced only during post-hemorrhage period in the NH group. In contrast, MABP was reduced at 20 min of hemorrhage in the HH group. Post-hemorrhage MABP was not different between groups. VP responses mirrored MABP responses with HH group greater than NH group at 20 and 30 min of blood loss, but not post-hemorrhage. PRA increased after 20 min of blood loss in NH group and remained elevated. PRA was increased after 20 and 30 min of blood loss in the HH group. ANP was reduced in both groups. It appears hemorrhage during hypoxia results in an earlier development of hypotension.

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ACETAZOLAMIDE vs DEXAMETHASONE FOR PREVENTION OF ACUTE MOUNTAIN SICKNESS: A META-ANALYSYS

Ellsworth, A.J., Ried, L.D., Carter, K., Nuovo J., Larson E.B. Universities of Washington and Florida, Seattle, WA and Gainsville, FL

Despite the effectiveness of slow, staged ascent, the best method of preventing acute mountain sickness (AMS), interest continues in developing a prophylactic drug regimen which is rapid-acting, effective, and well tolerated. Most experience has been with acetazolamide. More recently, dexamethasone has also been found to prevent the symptoms of AMS. A computer-assisted literature search followed by an ancestry approach to the references of pertinent articles, and personal communication with investigators in the field yielded 27 reports meeting inclusion criteria (controlled trial, human subjects, studies conducted at altitude - chamber or field, prophylaxis rather than treatment of AMS, and the presence of clinical outcome criteria). The results of these 27 trials were reanalyzed and pooled. The authors definition of AMS was used throughout. The average weighted effect size when both drugs' results are pooled was -0.55 (95% CI = -0.30 to -0.80 (average sample size = 30). When examined individually, weighted effect size for prophylaxis with acetazolamide was -0.55 (95% CI = -0.20 to -0.90) from 19 studies with an average sample size of 32 subjects and -0.47 (95% CI = -0.04 to -0.89) with an average sample size of 28 subjects in 8 studies of dexamethasone. Overall, pharmacologic prophylaxis is effective. Acetazolamide and dexamethasone appear to be nearly equally effective. Only one head to head comparative report was found. Varying definitions of AMS made analysis difficult. More work needs to be done to unequivocally determine comparative effectiveness of these two agents.

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THE EVENT RELATED POTENTIALS AND THE AUDITORY EVOKED POTENTIALS IN THE HUMAN BRAIN AT HIGH ALTITUDE

Endo,K., M.Adachi, A.Demizu, K.Hirata, Y.Jinnouchi, N.Kan, S.Kubo, Li-Syuping, K.Matsubayashi, K.Matubayashi, T.Matsuzawa, R.Nagata, M.Nakashima, A.Saito, S.Seto, T.Sugie, and T.Tobe.
Kyoto University Himalayan Medical Research Expedition, Faculty of Medicine, Department of Physiology, Sakyo-ku, kyoto 606, Japan.

The aim of this study was to find the changes in the electrical activities of the human brain at high altitude, occurring in association with the brain functions and disorders. Electroencephalogram (EEG) was recorded from the expedition members, at vertex (Cz) on the scalp of the subjects, with earlobes as reference. The amplified EEG was stored on magnetic tapes for off-line analysis by an averaging computer after returning to our laboratory. The subjects concentrated to a tone and responded by pressing a push-button with the thumb. It was found that late component of the auditory evoked potential (AEP) and the event related potential (P300) decreased at high altitude. Mean values of the late P2-N2 component of AEP were 9.6 ± 5.8 μV (S.D.) at high altitude and 15.8 ± 6.2 μV at sea level (N=21). Mean values of P300 were 7.9 ± 5.1 μV at high altitude and 18.5 ± 9.2 μV at sea level (N=13), respectively. The decrease in the size of P300 at high altitude was closely associated with the occurrence of retinal hemorrhage.

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